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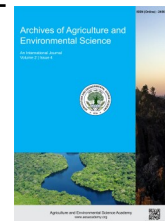


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## REVIEW ARTICLE



# A review on aflatoxins in stored grain food, their sources, mechanisms and possible health hazard

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## ABSTRACT

The aflatoxin producing fungi *Aspergillus flavus*, *Aspergillus parasiticus*, and *Aspergillus nomius* are highly hepatotoxic, carcinogenic and immunosuppressive which can spread quickly in environment and contaminate stored food. It can lead to serious threats to both human and animal health hazards by causing various diseases. Aflatoxin can breakdown DNA and causes genomic damage during cell division, leading to cancer even death where these breakdown products accumulate in the liver. The chemistry and biosynthesis process of the aflatoxin is discussed in present review study in a nutshell along with their occurrences and the health hazards to human. This review focuses on sources, production, biosynthesis, toxicology, detection, and control techniques of aflatoxins to assure food safety. Present review study is valuable as it provides knowledge on aflatoxins toxicity which helps in food security and safety as well as reduces human diseases in future.

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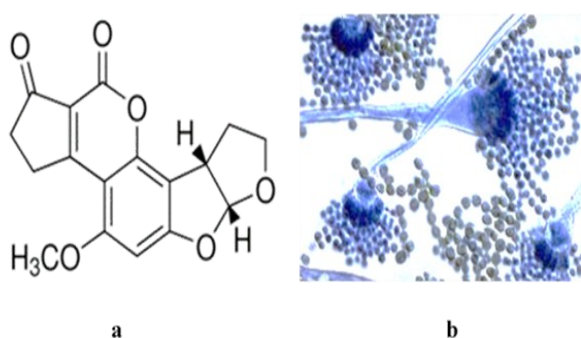
## INTRODUCTION

Aflatoxins are mostly toxic secondary fungal metabolites which are derived from some certain strains of fungi such as species of *Aspergillus*, specifically *Aspergillus flavus*, *Aspergillus parasiticus* (Figure 1) (Giray *et al.*, 2007; Kumar *et al.*, 2008) and that can quickly absorb by blood cells in human body if consume any aflatoxin contaminated food. Aflatoxins also known as potent and harmful groups of mycotoxins. Aflatoxin B<sub>1</sub> (AFB<sub>1</sub>), AFB<sub>2</sub>, AFG<sub>1</sub> and AFG<sub>2</sub> are found mostly in nature and more than 20 types of aflatoxin identified (Figure 2) (Giray *et al.*, 2007). The most important foods such as wheat, maize, rice, groundnuts, dried fruit, pearl millet, tree nuts (almonds, pecans, walnuts), black pepper, coriander, turmeric, zinger cocoa beans etc. are mostly contaminated by aflatoxins (Giray, *et al.*, 2007; Bbosa, *et al.*, 2013; Smith *et al.*, 2015). Highly vulnerable crop in Bangladesh

that contaminated by aflatoxins is maize (67%), it was collected from farmers' stored grain in which average aflatoxin B<sub>1</sub> content found 33 microg/kg and maximum was found 245 microg/kg (Dawlatana, 2002). AFB<sub>1</sub> was identified in 58 organic spice and 32 organic herb samples, among organic spice samples and organic herbs sample, the maximum concentration of AFB<sub>1</sub> was detected respectively in cinnamon sample (53 µg/kg) and rosehip sample (52.5 µg/kg) (Tosun and Arslan, 2013). These types of fungi are also commonly found in stored agricultural commodities such as corn, millet, sesame seeds, sorghum, sunflower seeds and different types of spice for keeping in improper storage (Figure 3). If this infected food (with aflatoxins containing fungi) is processed, then aflatoxins can enter the processed food and that are harmful for human health and also animals by affecting several problems. Children are frequently suffered by the exposure of aflatoxins, which results to stunted

growth, delayed growth and development (Turner et al., 2007; Voth-Gaeddert et al., 2018), liver damage and finally liver cancer. Adults are capable to tolerate a higher level of aflatoxins exposure, but they should be conscious. The symptoms of severe aflatoxicosis include hemorrhagic necrosis of the liver, bile duct proliferation, edema, lethargy and death also observed (Williams et al., 2004; Kumar et al., 2008). It was firstly conscious in the Spring of 1960 by discovering the main cause of "turkey X disease" in Great Britain, England (Wannop, 1961). *A. flavus* responsible for some common clinical syndromes such as granulomatous sinusitis, keratitis, cutaneous aspergillosis, wound infection, osteomyelitis following trauma and inoculation, it also acts as agent of otitis, keratitis, pulmonary and systemic infec-

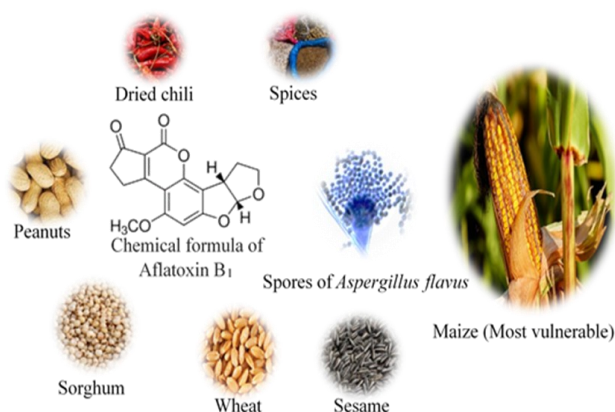
tions in immunocompromised patients (Hedayati et al., 2007). Aflatoxins contaminated food cannot be destroyed by normal process of cooking (Kumar et al., 2017). Enzymes of liver can breakdown aflatoxins and the breakdown products intercalate DNA and causes genomic damage during cell division that causes to cancer where these breakdown products accumulate in the liver to create liver cancer. It also estimated that due to harmful effect of aflatoxins, approximately 25% of agricultural products damaged worldwide (Yard, 2013). A research conducted by International Agency for Research on Cancer (IARC) in 1993 and informed that aflatoxins are class 1 toxic chemical compounds and responsible for causing human carcinogen, here given characteristics of aflatoxins in Table 1 (Kumar et al., 2008).



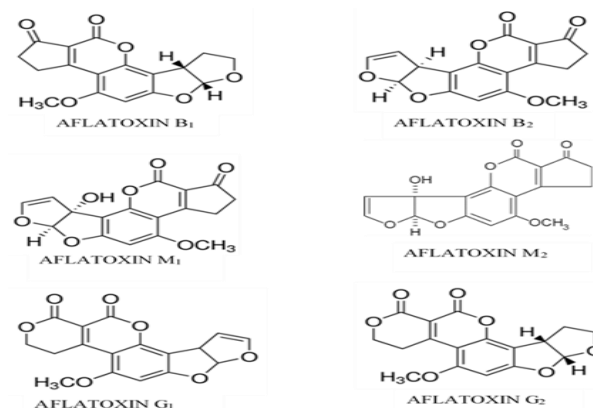
**Figure 1.** (a). Chemical formula of aflatoxin B<sub>1</sub> (b). Spores of *A. flavus* seen under microscope.

### Sources of aflatoxins producing fungi

*Aspergillus flavus*, *A. parasiticus*, and *A. nomius* (Kurtzman et al., 1987) are the major source of different aflatoxin which are commonly grow in soil, particularly oil-rich seeds, grains living plants (Geiser et al., 2000) vegetation that decayed, crops residue such as hay, deterioration of microbiological activity and favorable environmental conditions more than 7% moisture and 20°C temperature. Many agricultural crops along with agricultural commodities are contaminate by these types of fungi during improper and delayed harvesting and post harvesting, storage and in processing. Corn and peanuts mostly contaminated by *A. flavus* and *A. parasiticus* respectively.



**Figure 3.** Crops that mostly contaminated by the species of *Aspergillus*.



**Figure 2.** Several chemical structures of common aflatoxins found in stored grain foods.

**Table 1.** Characteristics of aflatoxins.

Effects	Characteristics of aflatoxins
Acute or chronic effects	Synergistic
	Mutagenic
	Carcinogenic
	Cytotoxic
	Hepatotoxic
Effects of aflatoxins in molecular level	DNA mutations (Genetic disorder)
	Inhibit transcription and translation
	Proteins and nucleic acids cannot synthesize properly
	Genotoxic
	Inhibit normal process of Electron transport chain

Source: (Krishnamachari et al., 1975; Niranjana et al., 1982; Hsieh, 1987; Doi et al., 2002; Verma, 2004; Peterson et al., 2006; Hussain et al., 2007; Groopman et al., 2008; Wu et al., 2009)

### Favorable environment for growth of aflatoxins producing fungi and their expression

Optimum growth of *Aspergillus parasiticus* was analyzed at 35°C in the ranges 17–42°C temperature with varying combinations of 0.90–0.99 water activity ( $a_w$ ), that stimulate the regulatory genes' (aflR/aflS) expression levels and production of aflatoxin in *A. flavus* and *A. parasiticus* (Schmidt-Heydt et al., 2010). *A. flavus* can survive at temperature ranging from 12°C to 48°C (Hedayati et al., 2007). Water activity ( $a_w$ ) and optimum temperature have remarkable effect on species of *Aspergillus* and production of aflatoxins (Sanchis and Magan, 2004). The growth and production of AFB<sub>1</sub> of *A. flavus* decreases under the temperature to 37°C during water stress. It was reported that growth of fungal biomass and AFB<sub>1</sub> production was highest at 28°C temperature and 0.96 water activity, while no prominent fungal growth and AFB<sub>1</sub> production detected at 20°C with the dried state condition at 0.90 and 0.93 water activity (Gallo et al., 2016; Kumar et al., 2017). Reverse transcriptase quantitative PCR also showed that in 28°C the two genes (aflR/aflS) were expressed highly and the greatest accumulation of fungal biomass appeared, while the lowest level of expression was detected at 20 and 37°C, concluded that variation in temperature and in water activity ( $a_w$ ) plays very significant role in genes expression rate and production of aflatoxin (Gallo et al., 2016; Kumar et al., 2017).

### Chemistry and biosynthesis of aflatoxins in human body by the species of *Aspergillus*

Different genes and enzymes that present in some species of aflatoxin producing fungi mainly in *Aspergillus flavus* also in *Aspergillus parasiticus* with factors affecting aflatoxin production have been reviewed (Yabe and Nakajima, 2004; Yu, 2012). About 30 aflatoxin pathway and 6 transcripts are identified through *Aspergillus flavus* EST and process about the Conversion of Acetate to Norsolorinic Acid (NOR) (Yu, 2012). A research conducted to investigate aflatoxin biosynthesis pathway by using cell-free enzyme systems prepared from *Aspergillus parasiticus* and elucidation about the novel metabolic grid that catalyzed by a new cytosol monooxygenase enzyme involved in aflatoxin biosynthesis (Yabe et al., 2003). A detailed study reviewed about biosynthesis and regulation of aflatoxins for reducing human exposure to aflatoxins as well as in how aflatoxin impacts human health (Roze et al., 2013).

### Molecular targets of aflatoxin in human body

Normal function of gene expression and protein synthesis, normal metabolic activity inhibited by the effects of aflatoxin (Figure 4) (Kiessling, 1986). Mitochondrial respiration, cellular energy production, synthesis of macromolecule decreases by the effect of aflatoxins (Hsieh, 1987; Dhanasekaran et al., 2011). Somatic mutations progress by aflatoxins in the p53 tumor suppressor gene (TP53) results to several genetic and epigenetic changes in the molecular pathogenesis of HCC (Hussain et al., 2007), p53 gene regulates the transcription of protective antioxidant genes and extensive DNA damage (Hussain et al.,

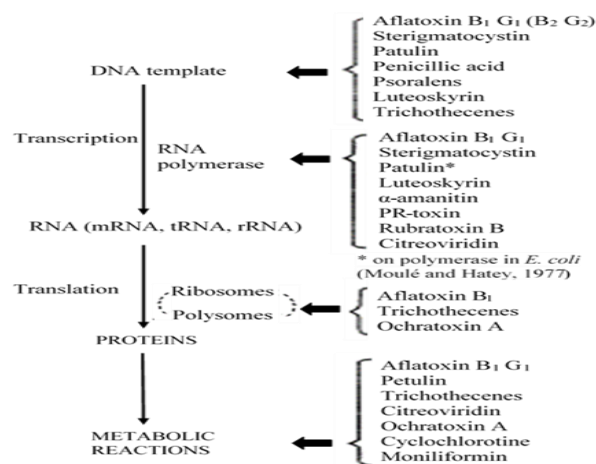


Figure 4. Mycotoxins affecting major sites in RNA and protein synthesis (adopted from Kiessling, 1986).

2007). Aflatoxins are inhibitors of nucleic acid synthesis because they have a high affinity for nucleic acids and polynucleotides that affect improper formation of organelles, DNA and other important metabolites (Dhanasekaran et al., 2011), so they cause several abnormalities in the structure and functioning of mitochondrial DNA and brain cells which are mainly due to adduct formation with DNA, RNA and protein, results to hepatotoxic, hepatocarcinogenic and mutagenic effects (Verma, 2004). Aflatoxin B<sub>1</sub> is capable of weak binding with single-stranded DNA but purine bases and amino group play a vital role in the binding of all the aflatoxin to DNA (Clifford and Rees, 1967). Interaction of aflatoxin B<sub>1</sub> with DNA investigated in more detail by the difference spectra of aflatoxin, mixed with various nucleosides and the results indicate that for the binding of aflatoxin to DNA the purine ring is important and the presence of an amino group on the ring also aids in the interaction (Clifford and Rees, 1967).

### Metabolism and mechanisms of aflatoxin B<sub>1</sub> in liver

Different types of enzymes remain in human liver and intestine, these microsomal enzymes induce to metabolize aflatoxin B<sub>1</sub> into other different metabolites through hydroxylation, hydration, demethylation and epoxidation (Figure 5), such as CYP450 enzymes can bioactivate AFB<sub>1</sub> to an electrophilic, highly reactive and unstable metabolite that can react with cellular molecules such as DNA (causing genotoxicity), proteins (causing cytotoxicity in the cell of Hepa-1) and also produce Aflatoxicol if cytoplasmic reductase enzyme acts on aflatoxin B<sub>1</sub> (Doi et al., 2002; Dohnal et al., 2014). CYP1A2 and CYP3A4 enzymes also catalyzes biotransforming of AFB<sub>1</sub> to the toxic product AFB<sub>1</sub>-8,9-epoxide (AFBO) that is hepatocellular cancerogenic in nature and this process occurs through epoxidation and hydration of aflatoxin B<sub>1</sub>, which binds to DNA and alters gene expression they also cause lipids accumulation in the liver that results to liver very fatty (Dhanasekaran et al., 2011; Dohnal et al., 2014). Almost four metabolic pathways involve in toxic effect of AFB<sub>1</sub>, that are O-dealkylation to AFP<sub>1</sub>, ketoreduction to Aflatoxicol (AFL), epoxidation to AFB<sub>1</sub>-8,9-epoxide (highly toxic, mutagenic, and carcinogenic), and hydroxylation to AFM (highly toxic), AFP<sub>1</sub>, AFQ<sub>1</sub> and AFB<sub>2a</sub> (all relatively nontoxic) (Wu et al., 2009).

### Effects of aflatoxins on carbohydrate and lipid metabolism

Aflatoxins (Aflatoxin B<sub>1</sub>) are harmful on oxidative phosphorylation of carbohydrate metabolism that reduced hepatic/liver glycogen and raise blood glucose levels by accelerating oxidation of glucose 6-phosphate, also involve in decreasing activities of glycogen phosphorylase, phosphoglucomutase which reversibly converts glucose 6-phosphate into glucose 1-phosphate (Figure 6) (Shankaran et al., 1970; Kiessling, 1986). Lipid metabolism cannot complete properly due to presence of aflatoxins that inhibits glycogen synthesis by decreasing enzymatic activities of glycogen synthetase and transglycosylase, these enzymes helps to catalyze elongation and rearrangement of the glycogen molecules and the experiment was checked in chickens (Shankaran et al., 1970; Tung et al., 1983). Additionally, hepatic glycogen reduces by accelerating glucose 6-phosphate oxidation (Kiessling, 1986).

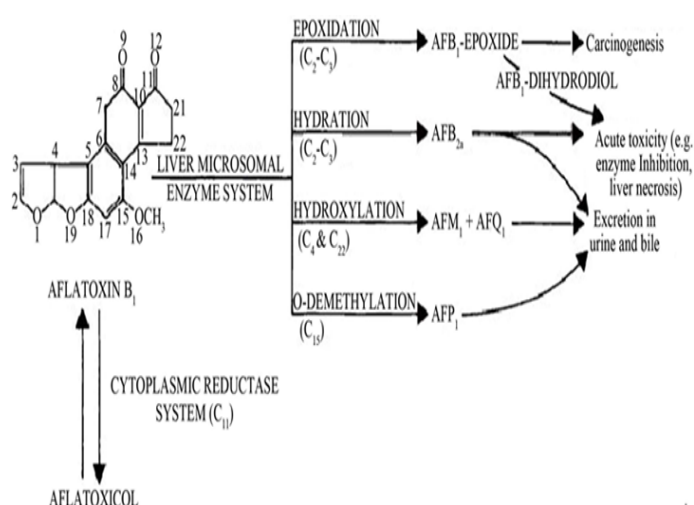


Figure 5. Metabolism of aflatoxins in liver (adopted from Dhanasekaran et al., 2011).

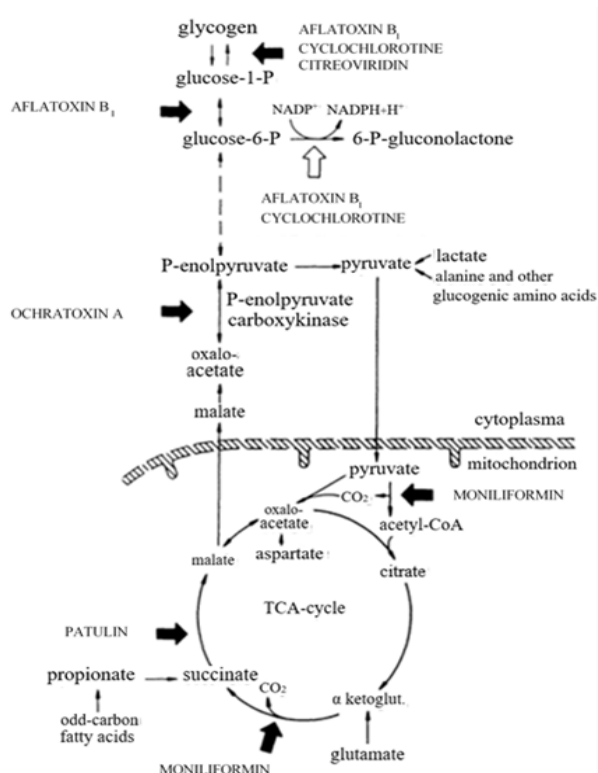


Figure 6. Sites where mycotoxins interfere with carbohydrate metabolism (adopted from Kiessling, 1986).

### Effects of aflatoxins on electron transport chain (ETS) in mitochondria

Aflatoxin B<sub>1</sub> inhibits the vital function of electron transport system in mitochondria at site II in cytochrome oxidase level, whereas the inhibition occurs between cytochrome b1 (cyt-b1) and c (Figure 7) (Kiessling, 1986). It was reported that AFB<sub>1</sub> are capable of covalently binding to mitochondrial DNA with a 3 to 4 times higher affinity than nuclear DNA, and the chemical modification or concentration of carcinogen adducts in mitochondrial DNA persists even after 24 hours, possibly because of lack of excision repair mechanisms (Niranjan et al., 1982). This effect results to mitochondrial transcription and translation that remain inhibited up to same time and suggested that it may happen for long-term effects of aflatoxin B<sub>1</sub> on the genetic system of mitochondria (the power house of cell) (Niranjan et al., 1982). Another research also reported that lesions (a region in an organ or tissue which has suffered damage) in mitochondrial DNA are persistent, possibly lack of same mechanisms in the organelle, results to inhibition of mitochondrial transcription and translation (Hsieh, 1987).

### Effect of aflatoxin on Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) that induced to liver failure

If individuals affect by both interaction of aflatoxin B<sub>1</sub> and hepatitis B virus (HBV) in same time leads to enhance the development of hepatocellular carcinoma (HCC) (Figure 8) (Groopman et al., 2005; Hussain et al., 2007). It happens about 30 times greater than the risk in individuals exposed to only aflatoxin (Groopman et al., 2008; Liu and Wu, 2010). Synergistic effect of aflatoxins appeared on hepatitis C virus that induced liver cancer (Kirk et al., 2006; Wild and Montesano, 2009; Liu and Wu, 2010). A research analyzed that there is a correlation with the presence of aflatoxins and increased liver cancer in individuals who are carrier of hepatitis B (Dhanasekaran et al., 2011). These viruses (HBV and HCV) induce liver injury, hepatocyte death and promote hepatocarcinogenesis (Hussain et al., 2007). A review explored about the independent and combined effects of hepatitis B virus (HBV), hepatitis C virus (HCV) and aflatoxin exposure responsible in the causes of HCC (Kirk et al., 2006).

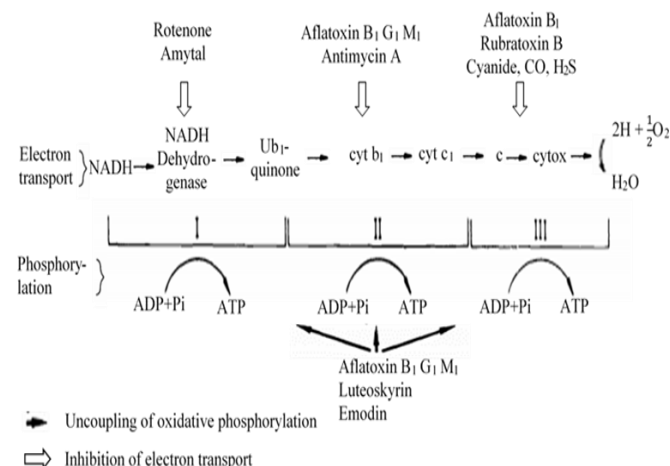
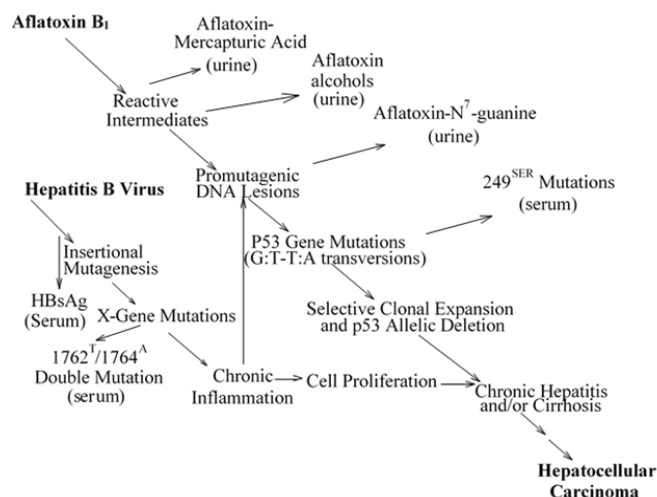


Figure 7. Aflatoxin inhibition of electron transport chain in oxidative phosphorylation (adopted from Kiessling, 1986).

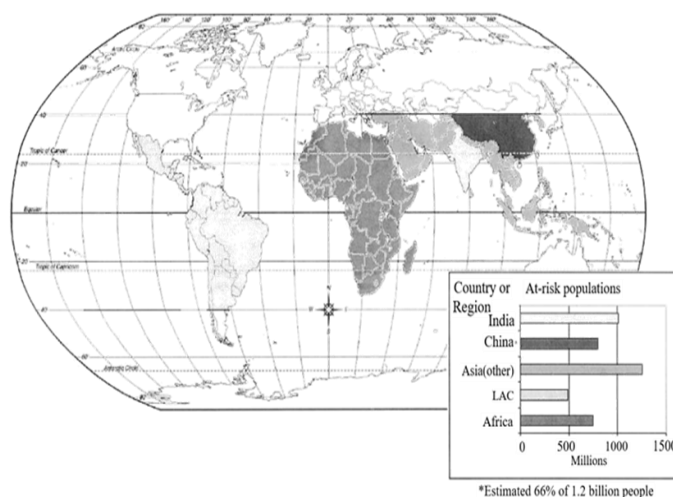




**Figure 8.** Potential molecular mechanisms of interaction between HBV and aflatoxin in the development of hepatocellular carcinoma, as elucidated by several biomarkers. HBsAg, hepatitis B surface antigen (adopted from Groopman et al., 2005).

### Toxicity and toxic effect of aflatoxins in human health

The severe or acute lethal dose of aflatoxins for adults is 10 to 20 mg and the median lethal dose is 0.36 mg/kg in total body weight (Etzel, 2002; Dhanasekaran et al., 2011). The clinical manifestations of aflatoxicosis or disease symptoms are fever, malaise and anorexia followed with abdominal pain, high colored urine, vomiting, and edema of feet, Jaundice, rapidly developing Ascitis, pulmonary edema, portal hypertension, high mortality with sudden death, childhood cirrhosis, increases risk with a synergistic effect, swollen of gall bladder, decrease in Vitamin K activities (Krishnamachari et al., 1975; Groopman et al., 2008). Most people are at risk of chronic exposure around the world (Figure 9) (Dhanasekaran et al., 2011). Major histopathological diagnosis reported gastrointestinal bleeding, fatty infiltration, hepatic lesions, even hepatomas bile duct proliferation with periductal fibrosis and centrilobular necrosis (Krishnamachari et al., 1975; Ngindu, et al., 1982; Groopman et al., 2008; Yu, 2012).



**Figure 9.** Areas and populations at risk of chronic exposure to uncontrolled aflatoxin. LAC, Latin America and the Caribbean (adopted from Williams et al., 2004).

### Outbreaks due to effect of aflatoxins

At first, aflatoxins were isolated from turkeys and recognized as the harmful toxins of turkey "X" disease in England and the affected birds died quickly (Wannop, 1961). In 1974, a major outbreak of hepatitis due to aflatoxin was reported in the states of Gujarat and Rajasthan in Western India, resulting in an estimated about 397 affected and 106 deaths for consuming of maize that was heavily contaminated by aflatoxin (Krishnamachari et al., 1975). Aflatoxin B<sub>1</sub> was detected in high concentration in the livers of those affected individuals who died and the outbreaks lasted for two months (Krishnamachari et al., 1975). Some Kenyan people also suffered in 1981 due to toxic effect of aflatoxin and number of affected and dead was 20 and 12 respectively (Ngindu et al., 1982). It was estimated that annually about 250,000 deaths occur in certain parts of China and sub-Saharan Africa due to hepatocellular carcinoma where high presence of aflatoxin in food (Yabe and Nakajima, 2004). The toxicity, toxic effect and outbreaks due to harmful impact of aflatoxins given at a glance in Table 2.

**Table 2.** Toxicity, toxic effect and outbreaks due to harmful impact of aflatoxins.

Toxicity, toxic effect and outbreaks due to harmful impact of aflatoxins							
Country	Affected	Dead	Symptoms and signs	Exposure			Major histopathology of liver
				Source	Duration (days)	Toxin (Aflatoxin B <sub>1</sub> )	
Western India in 1974	397	106	Jaundice, ascites, portal hypertension, and high mortality rate with sudden death	Maize	60	6.25-15.6 ppm	Gastrointestinal bleeding, bile duct proliferation with periductal fibrosis
Kenya in 1981	20	12	Jaundice, afebrile or with low grade fevers, and extremely weak gastrointestinal bleeding	Maize	Several weeks	12 ppb at liver necropsy result contained up to 89 ppb.	Centrilobular necrosis

Source: (Krishnamachari et al., 1975; Ngindu et al., 1982)

### Detection techniques of aflatoxins

Presence of aflatoxins can be detected and identified according to their absorption and emission spectra, with peak absorbance occurring at 360 nm wave length. AFB toxins exhibit blue fluorescence at 425 nm wave length, while AFG toxins show green fluorescence at 540 nm wave length under UV radiation. This fluorescence phenomenon is widely accepted for aflatoxins detection while high performance liquid chromatography (HPLC), Liquid chromatography mass spectroscopy (LCMS), and enzyme linked immune-sorbent assay (ELISA) are the methods mostly used for its detection (Andrade et al., 2013; Sulyok et al., 2015; Kumar et al., 2017). Enzyme-linked Immunosorbent Assay (ELISA) used to identify aflatoxins based on estimation of AFB<sub>1</sub>-lysine (metabolite of AFB<sub>1</sub> toxin) concentration in the blood and the test can mainly detect the levels of AFB<sub>1</sub> in blood and can be used in detection of hepatitis B virus (Kumar et al., 2017).

### Management and control approaches

*Bacillus subtilis*, *Lactobacillus* spp., *Pseudomonas* spp., *Ralstonia* spp. and *Burkholderia* spp. are effective as bio control agents to control aflatoxin producing *Aspergillus flavus* (Palumbo et al., 2006). A research was conducted to examine antagonistic activity against *Aspergillus* section *Flavi* strains by selecting bacterial isolates from the non-rhizosphere of maize soil have been reported that strains of *Bacillus subtilis* and *Pseudomonas solanacearum* eliminated aflatoxin accumulation (Nesci et al., 2005). Several researches conducted about commodity-wise aetiology and contamination process about some crops such as groundnut, rice, maize, sorghum, spices and chilli (Kumar et al., 2008). Good agricultural practices and postharvest methods such as timely planting, providing adequate plant nutrition, controlling weeds, crop rotation, lowering moisture content during storage ( $\leq 8\%$  moisture level), adding preservatives to prevent insect infestation and fungal contamination during storage, sorting of contaminated pods and kernels, re-drying of groundnut pods and kernels, appropriate storage conditions to avoid favorable conditions for mold growth, avoidance of re-humidification of pods, detoxification of contaminated products, enhancing awareness of smallholders which effectively control *A. flavus* infection in the field and agricultural commodities, the study was conducted in groundnut (Waliyar et al., 2013). Some resistance-associated proteins of maize kernel endosperm that regulated by specific gene were identified by peptide sequencing and among them a stress-related peroxiredoxin antioxidant (PER1) was significantly induced upon *A. flavus* infection. Biotechnological approaches of genetic control and factors associated that affect biosynthesis of aflatoxin have been reviewed for aflatoxin management strategies (Yu, 2012). Genomic technology-based research developed for identification of the genes responsible for production and modification of the aflatoxin biosynthesis process (Cleveland et al., 2006; Holbrook et al., 2009). If a regular diet including apiaceous vegetables, such as carrots, parsnips, celery, parsley etc. can be maintained that are chemo-preventive and may reduce the carcinogenic effects of aflatoxin in humans (Peterson et al., 2006).

### Conclusion

Aflatoxins (mainly aflatoxin B<sub>1</sub>) are responsible for liver cancer that spread by contamination of *Aspergillus* spp. that mostly occurs by *Aspergillus flavus*. Outbreaks occur due to improper storage of agricultural commodities, lack of knowledge about the management of agricultural commodities and when we consume that contaminated food. In developing countries excessive levels of aflatoxins contamination in food requires major concern. Though, several techniques developed (physical, chemical, biological, and genetic engineering) that have been employed for the mitigation of aflatoxin, effective control and management need to be done for food safety worldwide.

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